

REMARKS

The Restriction Requirement and Election in the Parent Application

The parent application was restricted to one of the following inventions under 35

U.S.C. §121:

- I. Claims 1-10, drawn to a compound present in plants of the genus *Euphorbia* able to kill or inhibit the growth of cancer cells, or a composition containing a compound present in plants of the genus *Euphorbia* able to kill or inhibit the growth of cancer cells.
- II. Claims 11-15, 20-21 and 25, drawn to a method of treatment of a cancer, comprising the step of administering an anti-cancer effective amount of a compound present in plants of the genus *Euphorbia* or a composition comprising a compound present in plants of the genus *Euphorbia*.
- III. Claims 16-17, 20-21 and 25, drawn to a method of stimulating proliferation of non-neoplastic cells.
- IV. Claims 18, 20-21 and 25, drawn to a method of alleviating disease conditions by stimulating cells of the immune system.
- V. Claims 19-21 and 25, drawn to a method of inducing neoplastic cells to differentiate.
- VI. Claims 22 and 24-25, drawn to a method of preventing or alleviating damage to skin caused by ultraviolet irradiation, ionizing radiation, microwave radiation or exposure to ozone.

In the parent, in response to the Restriction Requirement, Applicant elected Group II, claims 11-15, 20-21 and 25, drawn to a method of treatment of a cancer, comprising the step of administering an anti-cancer effective amount of a compound present in plants of the genus *Euphorbia* or a composition comprising a compound present in plants of the genus *Euphorbia*.

Claims canceled and added in the instant amendment

Claims 1 to 32 are canceled, without prejudice, and new claims 33 to 99 are added. Thus, after entry of the instant amendment, claims 33 to 99 will be pending.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for new claims directed to methods wherein the compound is provided in the form of a ethanol extract obtained from the sap of a species of *Euphorbia* can be

found, *inter alia*, in Example 12, on pages 52 to 53. Support for new claims directed to methods wherein the compound is capable of inhibiting the growth of various cell lines, can be found, *inter alia*, on page 12, lines 20 to 26. Support for new claims directed to methods wherein the compound is provided in the form of an ethanol extract obtained from the sap of a species of *Euphorbia peplus*, *Euphorbia drummondii* or *Euphorbia hirta* can be found, *inter alia*, on page 12, lines 5 to 30. Support for new claims directed to methods wherein the compound can be a jatrophane, a jatrophane derivative or a pharmaceutically acceptable salt thereof, or a composition comprising a jatrophane ring conformation, including a composition is present in two diastereomeric conformations, can be found, *inter alia*, on Table 2, page 14 to 15; on page 42, line 27 to page 43, line 26; on page 45, line 15 to page 49, line 6. Support for new claims directed to methods wherein the compound can be a pepluane, a pepluane derivative and a pharmaceutically acceptable salt thereof, can be found, *inter alia*, on Table 2, page 14 to 15; on page 46, Table 15; page 47, lines 11 to 15. Support for new claims directed to methods wherein the compound can be a paraliene, a paraliene derivative and a pharmaceutically acceptable salt thereof can be found, *inter alia*, on Table 2, page 14 to 15; on page 13, lines 3 to 11. Support for new claims directed to methods wherein the compound can be an angeloyl-substituted ingenane, or a derivative of the angeloyl-substituted ingenane, or a pharmaceutically acceptable salt thereof, can be found, *inter alia*, on page 12, lines 5 to 35; Example 9, pages 43 to 45, e.g., page 45, lines 2 to 10; Example 10, pages 49 to 51, e.g., lines 23 to 25, page 49; Example 12, pages 52 to 53, e.g., lines 19 to 37, page 52. Support for new claims directed to methods of treating a human subject with cancer can be found, *inter alia*, on pages 60 to 61, Example 14. Support for new claims directed to methods of treating a human subject with various solid tumors, including cancers such as breast, prostate, cervical, lung and colon cancers can be found, *inter alia*, on page 16, lines 25 to 34. Support for new claims directed to methods of treating a subject with a cancer such as a melanoma, a Merkel cell carcinoma, a squamous cell carcinoma, a basal cell carcinoma and a solar keratosis, can be found, *inter alia*, on page 16, line 29 to page 17, line 12; Example 13, pages 55 to 57. Support for new claims directed to methods wherein the compound further comprises a beta-alanine betaine or a hydroxy-dimethyl proline, can be found, *inter alia*, page 16, lines 22 to 24.

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CONCLUSION

In view of the foregoing amendment and remarks, Applicant believes all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicant believes that no fee is required for submission of this Response. However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 06-1050. Please credit any overpayment to the above-noted Deposit Account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858 678 5070.

Respectfully submitted,

Date:

June 21, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicant : James Harrison Aylward Art Unit : to be assigned
Serial No. : to be assigned Examiner : to be assigned
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Title : ANTI-CANCER COMPOUNDS

In The Specification:

On page 1, after the title on line 1, under the heading, the following paragraph has been inserted:

--CROSS-REFERENCES TO RELATED APPLICATIONS

The present application is a continuation application of United States Patent Application Serial No. (USSH) 09/486,199, filed February 22, 2000, now pending, which was filed under 35 U.S.C. §371 based on PCT/AU98/00656, filed on August 19, 1998, which claims the benefit of priority to Australian Application No. PO-8640, filed August 19, 1997. These applications are explicitly incorporated herein by reference in their entirety and for all purposes.--

In The Claims:

The following new claims have been added:

33. A method of treating a subject with a cancer, the method comprising administering to the subject an effective amount of a compound,
- wherein the compound is derived from an extract from the sap of a species of *Euphorbia*, wherein the compound
- (a) is extractable from the *Euphorbia* sap in the presence of about 95% v/w ethanol,
 - (b) has cell inhibiting or retarding activity which is neither destroyed by acetone nor by heating at about 95°C for about 15 minutes, and
 - (c) is capable of inhibiting the growth of at least one cell line selected from the group consisting of MM96L, MM229, MM220, MM537, MM2058, HeLa, B16, LIM1215, A549, MCF7, MCC16 and Colo16.

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34. The method of claim 33, wherein the *Euphorbia* species is selected from the group consisting of *Euphorbia peplus*, *Euphorbia drummondii* and *Euphorbia hirta*.

35. The method of claim 33, wherein the compound comprises a composition selected from the group consisting of a jatrophane, a jatrophane derivative and a pharmaceutically acceptable salt of a jatrophane or a jatrophane derivative.

36. The method of claim 35, wherein the compound comprises a composition comprising a jatrophane ring conformation.

37. The method of claim 36, wherein the jatrophane ring containing composition is present in two diastereomeric conformations.

38. The method of claim 36, wherein the jatrophane ring containing composition is present in one diastereomeric conformation.

39. The method of claim 38, wherein the diastereomeric conformation is a conformation II.

40. The method of claim 36, wherein the composition comprising a jatrophane ring conformation comprises a nicotinate moiety.

41. The method of claim 36, wherein the composition comprising a jatrophane ring conformation comprises a benzoate moiety.

42. The method of claim 36, wherein the composition comprising a jatrophane ring conformation comprises a iso-butyrate moiety.

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43. The method of claim 33, wherein the jatropane derivative comprises an ester derivative.

44. The method of claim 33, wherein the jatropane derivative comprises an acetylated derivative.

45. The method of claim 36, wherein the jatropane derivative comprises a substitution in the jatropane ring carbon 1 position of a moiety selected from the group consisting of a -H and a -OAc.

46. The method of claim 36, wherein the jatropane derivative comprises a substitution in the jatropane ring carbon 2 position of a moiety selected from the group consisting of a -H, a -OAc and a CH₃.

47. The method of claim 36, wherein the jatropane derivative comprises a substitution in the jatropane ring carbon 3 position of a moiety selected from the group consisting of a -OH, a -OAc, a -OiBu (O(CH₃)₂CHCO), a -OCinn, a -OBz, a -OBzOCH₂CO, and a -PhCH₂CH₂CO₂.

48. The method of claim 36, wherein the jatropane derivative comprises a substitution in the jatropane ring carbon 4 position of an -H.

49. The method of claim 36, wherein the jatropane derivative comprises a substitution in the jatropane ring carbon 5 position of a moiety selected from the group consisting of a -OAc, a -OiBu (O(CH₃)₂CHCO), -OMeBu (OCH₃CH₂CH(CH₃)CO) and a -OAcAc.

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50. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 6 position of a moiety comprising an exocyclic double bond.

51. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 7 position of an -H₂, a -OAc, a -OiBu (O(CH₃)₂CHCO), a -OmeBu (OCH₃CH₂CH(CH₃)CO), a -OPr, a -OCOiPr and a -OCOEt.

52. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 8 position of an -H₂, a -OH, a -OAc, a -OiBu (O(CH₃)₂CHCO), a -OmeBu (OCH₃CH₂CH(CH₃)CO), a -OBz and a -OAng.

53. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 9 position of an -OH, a -OAc (-OCH₃CO), a -OCinn (OPhCHCHCO), a -ONic (C₅H₄NCO₂) and an = O.

54. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 10 position of a -(CH₃)₂.

55. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 11 and carbon 12 positions comprising a double bond between carbon 10 and carbon 11.

56. The method of claim 36, wherein the jatrophane derivative comprises a substitution in the jatrophane ring carbon 13 position of a -(CH₃).

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57. The method of claim 36, wherein the jatropha derivative comprises a substitution in the jatropha ring carbon 14 position of an -H, an -OH, a -OAc (OCH₃CO) and an = O.

58. The method of claim 36, wherein the jatropha derivative comprises a substitution in the jatropha ring carbon 15 position of an -OH and a -OAc (OCH₃CO).

59. The method of claim 35, wherein the composition comprises a 2,3,5,7,15-pentaacetoxy-9-nicotinoyloxy-14-oxojatropha-6(17),11E-diene (jatropha 1) or a pharmaceutically acceptable salt.

60. The method of claim 35, wherein the composition comprises a 2,5,7,8,9,14-hexaacetoxy-3-benzoyloxy-15-hydroxy-jatropha-6(17),11E-diene (jatropha 2) or a pharmaceutically acceptable salt.

61. The method of claim 35, wherein the compound comprises a 2,5,14-triacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxy-9-nicotinoyloxyjatropha-6(17), 11E-diene (jatropha 3) or a pharmaceutically acceptable salt of these.

62. The method of claim 35, wherein the compound comprises a 2,5,9,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxyjatropha-6(17),11E-diene (jatropha 4) or a pharmaceutically acceptable salt of these.

63. The method of claim 35, wherein the compound comprises a 2,5,7,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-9-nicotinoyloxyjatropha-6(17),11E-diene (jatropha 5) or a pharmaceutically acceptable salt of these.

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64. The method of claim 35, wherein the compound comprises a 2,5,7,9,14-pentaacetoxy-3-benzoyloxy-8,15-dihydroxyjatropa-6(17),11E-diene (jatrophane 6) or a pharmaceutically acceptable salt of these.

65. The method of claim 33, wherein the compound comprises a composition selected from the group consisting of a pepluane, a pepluane derivative and a pharmaceutically acceptable salt of a pepluane or a pepluane derivative.

66. The method of claim 65, wherein the pepluane derivative comprises an ester derivative.

67. The method of claim 65, wherein the pepluane derivative comprises an acetylated derivative.

68. The method of claim 65, wherein the pepluane derivative comprises a substitution in a position in a pepluane skeleton selected from the group consisting of

- an -H₂ or an -OAc (-OCH₃CO) at a carbon 1 position;
- a -CH₃ and an -H at a carbon 2 position;
- an -OBz at a carbon 3 position;
- an -H at a carbon 4 position;
- an -OAc (-OCH₃CO) at a carbon 5 position;
- a -CH₃ or an -CH₂OAc at a carbon 6 position;
- an -H₂ at a carbon 7 position;
- an -OAc (-OCH₃CO) or a double bond to C12 at a carbon 8 position;
- an -OAc (-OCH₃CO) or a double bond to C18 at a carbon 9 position;
- a -CH₃ and an -OAc (-OCH₃CO), a -CH₃, or a double bond to C11 at a carbon 10 position;
- an -H₂ or a double bond to C10 at a carbon 11 position;
- an -H or a double bond to C8 at a carbon 12 position;

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- a -CH₃ at a carbon 13 position;
- an -OAc (-OCH₃CO) at a carbon 14 position;
- an -OH at a carbon 15 position; and,
- an -H or an -H₂ at a carbon 18 position.

69. The method of claim 65, wherein the pepluane comprises a composition selected from the group consisting of a 5,8,9,10,14-pentaacetoxy-3-benzoyloxy-15-hydroxy-pepluane, a derivative of a 5,8,9,10,14-pentaacetoxy-3-benzoyloxy-15-hydroxy-pepluane and a pharmaceutically acceptable salt of a 5,8,9,10,14-pentaacetoxy-3-benzoyloxy-15-hydroxy-pepluane.

70. The method of claim 33, wherein the compound comprises a composition selected from the group consisting of a paraliane, a paraliane derivative and a pharmaceutically acceptable salt of a paraliane or a paraliane derivative.

71. The method of claim 70, wherein the paraliane derivative comprises an ester derivative.

72. The method of claim 70, wherein the paraliane derivative comprises an acetylated derivative.

73. The method of claim 70, wherein the paraliane derivative comprises a substitution in a position in a paraliane skeleton selected from the group consisting of

- an -H, an -H₂ or an -OAc (-OCH₃CO) at a carbon 1 position;
- a -CH₃ and an -H or a -CH₃ and an -OAc (-OCH₃CO) at a carbon 2 position;
- an -OBz at a carbon 3 position;
- an -H at a carbon 4 position;
- an -OAc (-OCH₃CO) at a carbon 5 position;

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a -CH₃ or a -CH₂OAc at a carbon 6 position;
an -H₂ at a carbon 7 position;
an -H or an -OAc (-OCH₃CO) at a carbon 8 position;
an = O at a carbon 9 position;
a -(CH₃)₂ at a carbon 10 position;
an -H₂ at a carbon 11 position;
an -H at a carbon 12 position;
a -CH₃ at a carbon 13 position;
an -OAc (-OCH₃CO) at a carbon 14 position; and,
an -OH at a carbon 15 position.

74. The method of claim 33, wherein the compound comprises a composition selected from the group consisting of a angeloyl-substituted ingenane, a angeloyl-substituted ingenane derivative and a pharmaceutically acceptable salt of a angeloyl-substituted ingenane or a angeloyl-substituted ingenane derivative.

75. The method of claim 74, wherein the angeloyl-substituted ingenane derivative comprises an ester derivative.

76. The method of claim 74, wherein the angeloyl-substituted ingenane derivative comprises an acetylated derivative.

77. The method of claim 74, wherein angeloyl-substituted ingenane is selected from the group consisting of a 20-O-acetyl-inganol-3-angelate, an acetylated derivative of a 20-O-acetyl-inganol-3-angelate and an ester derivative of a 20-O-acetyl-inganol-3-angelate.

78. The method of claim 33, wherein the cancer is a skin cancer.

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79. The method of claim 78, wherein the skin cancer is a malignant melanoma.

80. The method of claim 78, wherein the skin cancer is a Merkel cell carcinoma.

81. The method of claim 78, wherein the skin cancer is a squamous cell carcinoma.

82. The method of claim 78, wherein the skin cancer is a basal cell carcinoma.

83. The method of claim 78, wherein the skin cancer is a solar keratosis.

84. The method of claim 33, wherein the cancer is a solid tumor.

85. The method of claim 33, wherein the cancer is a lung cancer.

86. The method of claim 33, wherein the cancer is a colon cancer.

87. The method of claim 33, wherein the cancer is a prostate cancer.

88. The method of claim 33, wherein the cancer is a cervical cancer.

89. The method of claim 33, wherein the cancer is a breast cancer.

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90. A method of treating a subject with a cancer, the method comprising administering to the subject an effective amount of at least two compounds,

wherein the two compounds are derived from an extract from the sap of a species of *Euphorbia*, wherein the compounds

(a) are extractable from the *Euphorbia* sap in the presence of about 95% v/w ethanol,

(b) have cell inhibiting or retarding activity which is neither destroyed by acetone nor by heating at about 95°C for about 15 minutes, and

(c) are capable of inhibiting the growth of at least one cell line selected from the group consisting of MM96L, MM229, MM220, MM537, MM2058, HeLa, B16, LIM1215, A549, MCF7, MCC16 and Colo16.

91. The method of claim 90, wherein the compounds are selected from the group consisting of a jatropha, a jatropha derivative, a pharmaceutically acceptable salt of a jatropha, a pepluane, a pepluane derivative, a pharmaceutically acceptable salt of a pepluane, a paraliane, a paraliane derivative, a pharmaceutically acceptable salt of a paraliane, an angeloyl-substituted ingenane, an angeloyl-substituted ingenane derivative and a pharmaceutically acceptable salt of an angeloyl-substituted ingenane.

92. The method of claim 90, wherein the compounds are selected from the group consisting of a 5,8,9,10,14-pentaacetoxy-3-benzoyloxy-15-hydroxy-pepluane (pepluane), a derivative of a 5,8,9,10,14-pentaacetoxy-3-benzoyloxy-15-hydroxy-pepluane, a 2,3,5,7,15-pentaacetoxy-9-nicotinoyloxy-14-oxojatropha-6(17),11E-diene (jatropha 1), a derivative of a 2,3,5,7,15-pentaacetoxy-9-nicotinoyloxy-14-oxojatropha-6(17),11E-diene, a 2,5,7,8,9,14-hexaacetoxy-3-benzoyloxy-15-hydroxy-jatropha-6(17),11E-diene (jatropha 2), a derivative of a 2,5,7,8,9,14-hexaacetoxy-3-benzoyloxy-15-hydroxy-jatropha-6(17),11E-diene, a 2,5,14-triacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxy-9-nicotinoyloxy-jatropha-6(17),11E-diene (jatropha

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3), a derivative of a 2,5,14-triacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxy-9-nicotinoyloxy-jatropha-6(17),11E-diene, a 2,5,9,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxyjatropha-6(17),11E-diene (jatrophane 4), a derivative of a 2,5,9,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-7-isobutyroyloxyjatropha-6(17),11E-diene, a 2,5,7,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-9-nicotinoyloxyjatropha-6(17),11E-diene (jatrophane 5), a derivative of a 2,5,7,14-tetraacetoxy-3-benzoyloxy-8,15-dihydroxy-9-nicotinoyloxyjatropha-6(17),11E-diene, a 2,5,7,9,14-pentaacetoxy-3-benzoyloxy-8,15-dihydroxyjatropha-6(17),11E-diene (jatrophane 6), a derivative of a 2,5,7,9,14-pentaacetoxy-3-benzoyloxy-8,15-dihydroxyjatropha-6(17),11E-diene, a 20-O-acetyl-ingenol-3-angelate, a derivative of a 20-O-acetyl-ingenol-3-angelate and pharmaceutically acceptable salt of one or any combination of these compounds.

93. The method of claim 90, wherein the compounds are provided in the form of a chemical fraction obtained from the sap of a species of *Euphorbia*.

94. The method of claim 33, wherein the compound further comprises a beta-alanine betaine or a hydroxy-dimethyl proline.

95. The method of claim 33, wherein the compound is capable of inhibiting or retarding the growth of MM96L cells.

96. The method of claim 33, wherein the compound is capable of inducing differentiation of MM96L cells.

97. The method of claim 33, wherein the compound is capable of inducing normal melanocytes and/or T cells to proliferate.

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99. The method of claim 98, wherein the pharmaceutically- or cosmetically-acceptable carrier is selected from a β -alanine betaine hydrochloride and a t-4-hydroxy-N,N-dimethylproline.--

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Year	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	